



Alternative methods of toxicology

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<http://ecvam.jrc.it>

ECVAM



- Animal welfare directive 1986 (86/609/EEC)
- Established 1991, 61 staff members
- 16 alternative methods validated until 2002
- Business plan and reorganization 2003 responding to
7th amendment of the cosmetic directive 2003
emerging REACH legislation 2007
- 2005: (Q)SAR development to European Chemicals Bureau
- 9 methods validated 2006, 5 methods validated April 27th 2007
- Focus FP7: more drug, vaccine, food plus CORRELATE



Cosmetics industry and the 7th amendment



- EU: 2.000 companies, 60 billion € turnover
- EU: 5.000 new products per year, 25% turnover with products released within last 6 months
- Marketing ban if testing finished products or not using ECVAM-validated methods since 2003
- Phasing out ingredient testing with test and marketing bans in 2009 and 2013
- **Critical need for alternatives**



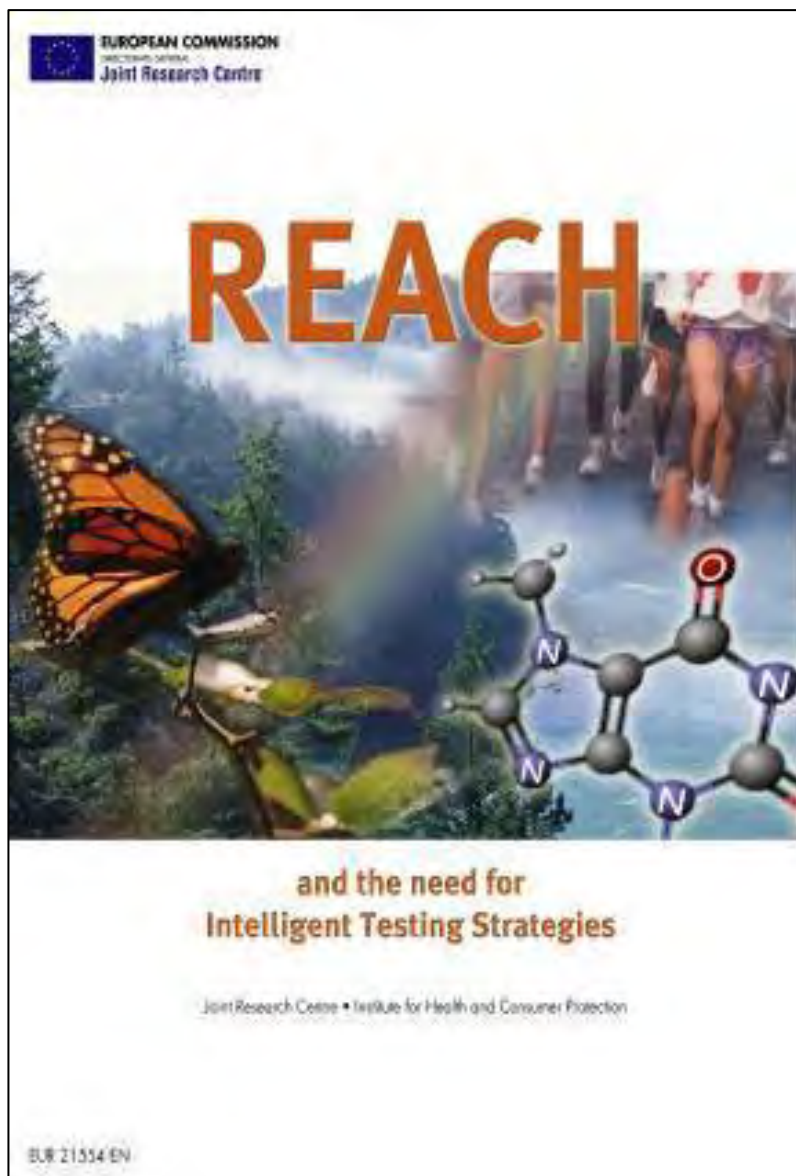
Chemical industry and REACH



- EU: 27.000 companies (96% SME), 590 billion € turnover = 33% of world market, 1,7 million employees
- EU: occupational skin disease cost 3 million work days per year, i.e. about 600 million €
- 86% of toxicological data on 'old' chemicals are lacking
- REACH will assess 30.000 chemicals marketed >1 ton/year
- Expected 180.000 preregistrations 2009, 70% of testing 2011-2017
- **Alternatives increase test throughput and reduce costs and animals**



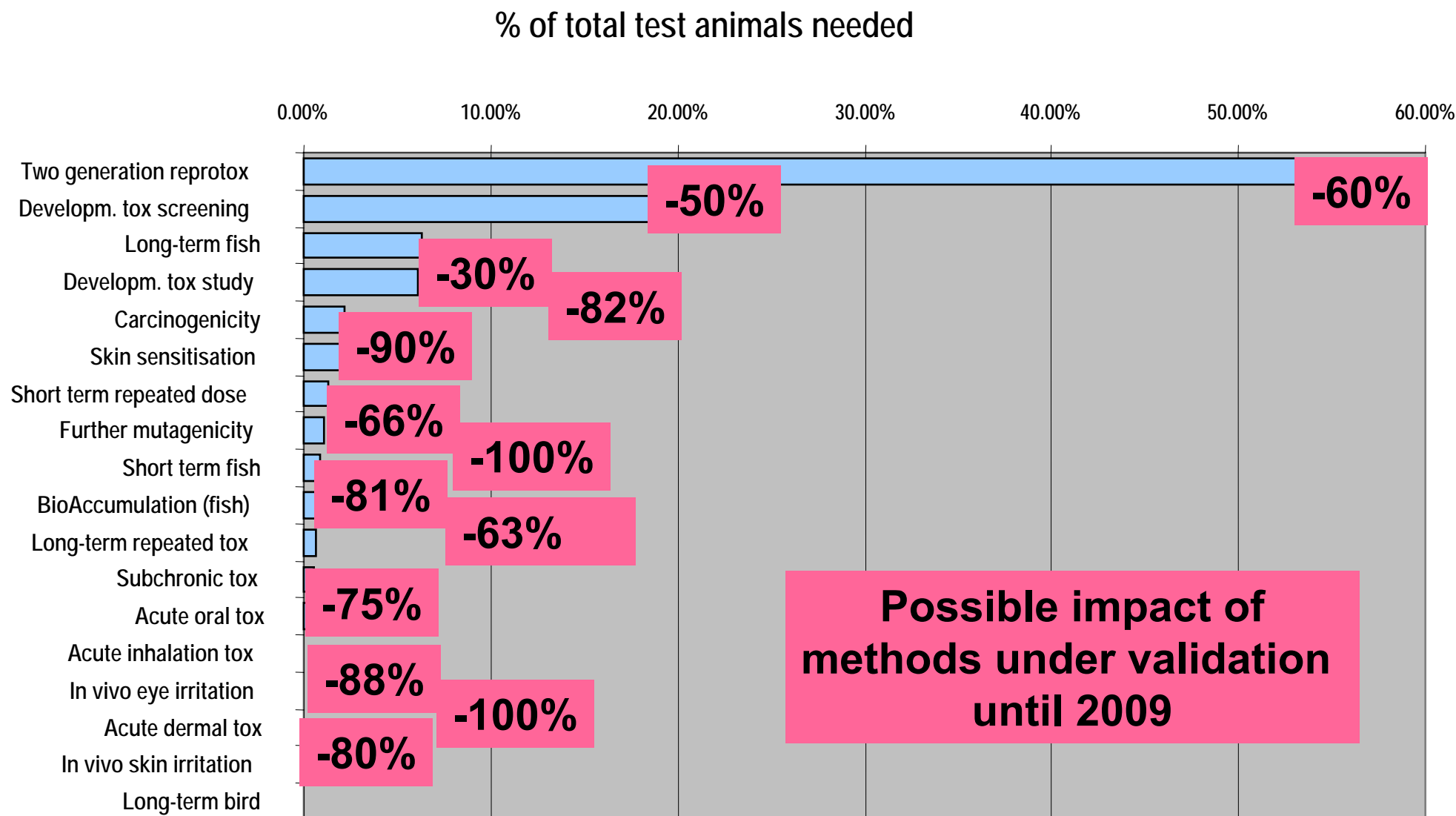
Test strategy development for REACH



- Key contribution to REACH implementation process
- CEFIC management, strong regulator and industry involvement, >200 experts
- ECVAM as coordinator for Commission
- About 2.000 pages ready May 2007
- **Many methods under validation already foreseen**



Estimated test animal need for the different endpoints





Topical toxicity



- Skin corrosion accepted OECD 2004, 3rd model validated 2006, 4th expected 2007
- Skin irritation validated 4'2007, me-too developments waiting
- Refinement for eye test under ESAC review, expected 2007
- 10 alternative for eye test under validation (8 retro- and 2 prospective), 2 validated for severe eye irritants 4'2007, rest expected 2008

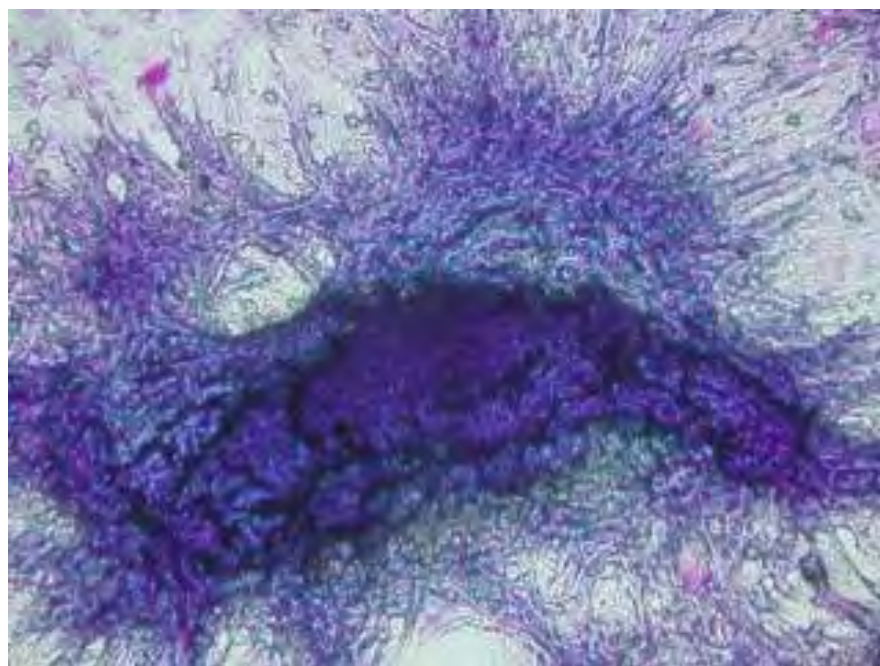


Systemic toxicity

- ECVAM/NICEATM study to predict starting dose by cytotox under review, human toxicity better predicted than by animal
- Prediction of non-toxic chemicals (70%) by cytotox under validation, expected 2008
- tiered test for dermal and inhalation
- A-Cute-Tox, expected 2009



Mutagenicity / Cancer



- 2 Cell transformation assays under validation, expected 2008, OECD TG in parallel
- Micronucleus validated 2006
- COMET assay under validation (lead JaCVAM)
- validation skin models for genotox
- Workshop false-positives, follow-up studies with COLIPA
- omission pos. control, peer-review prepared

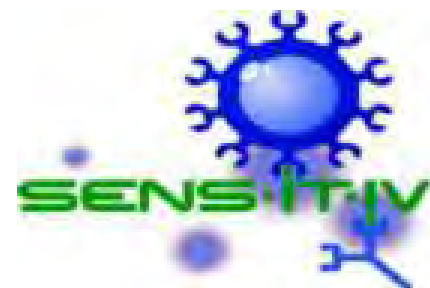




Sensitisation



- LLNA cut down approach under validated April 2007
- Three replacements to start validation 2007
- Non-radioactive LLNA under validation
- Sen-it-i.v.





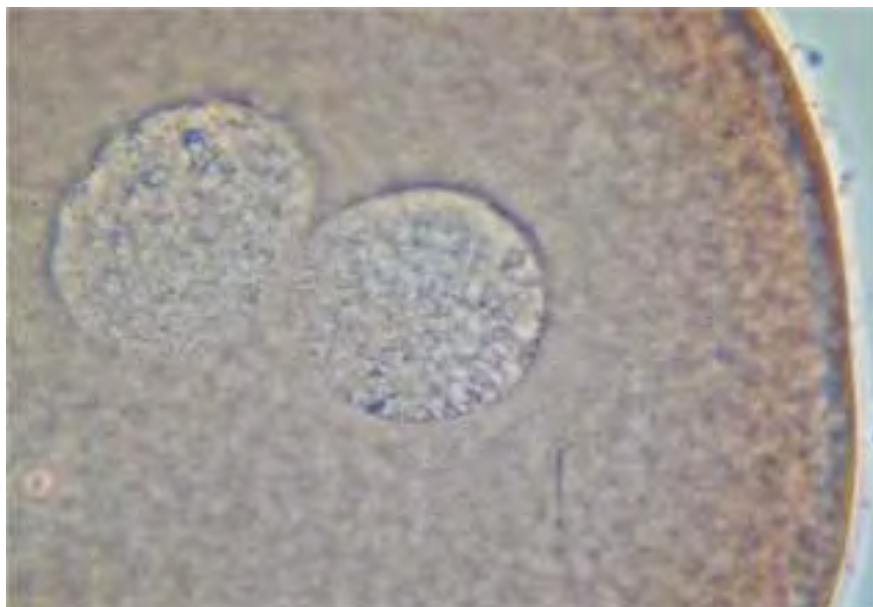
Ecotoxicology



- **Test strategy acute ecotox validated 2006**
- **Fish egg/embryo test prepared for peer-review, expected 2007**
- **Planned validation bioaccumulation with ILSI/HESI**



Reproductive toxicity

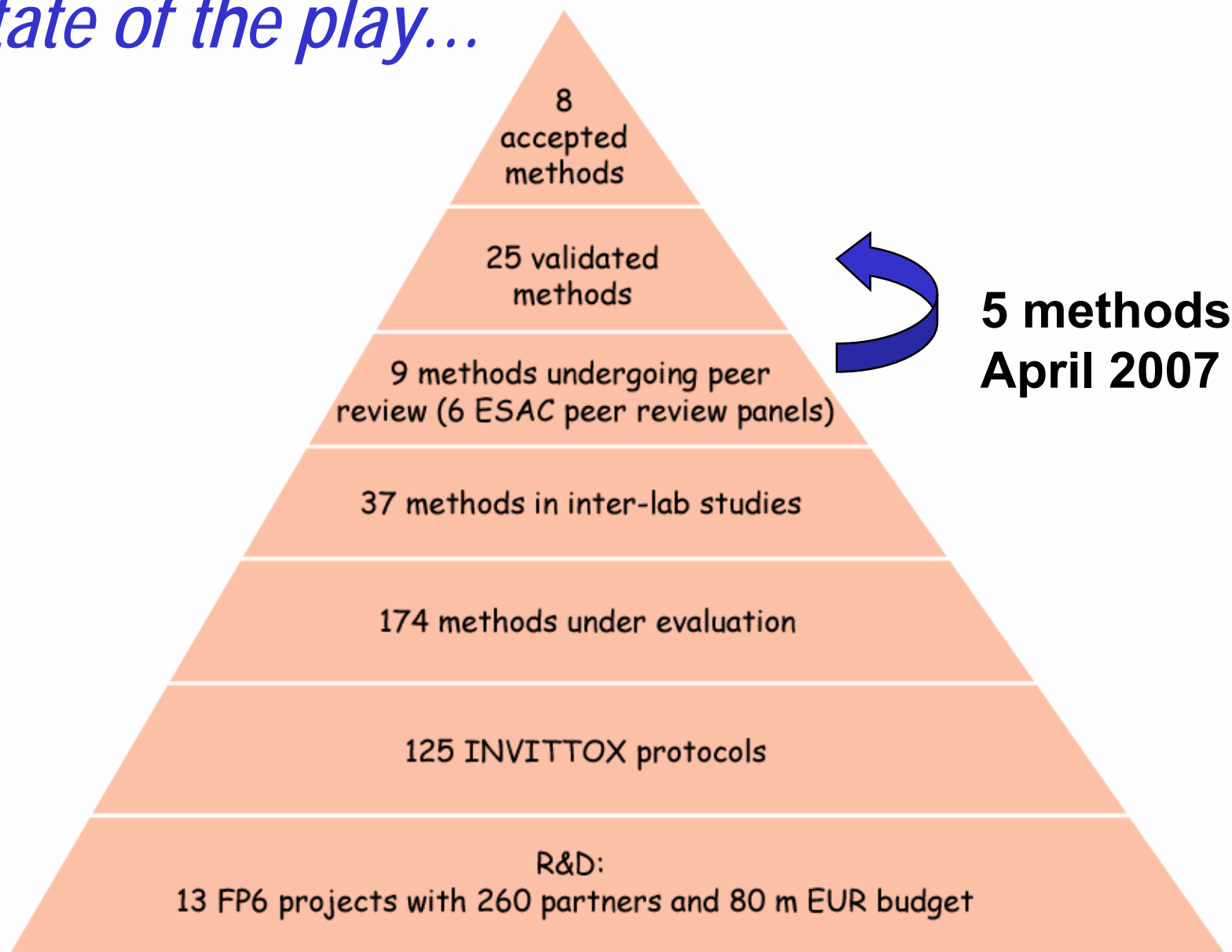


- Validated embryotoxicity tests to substitute for 2nd species and priority setting
- (extended) one-generation study under validation, expected 2008
- test battery for alerts under validation
- 11 endocrine disrupter tests under validation, expected 2008
- ReProTect





State of the play...





ECVAM DATABASE SERVICE
ON ALTERNATIVE METHODS TO
ANIMAL EXPERIMENTATION

Current Activities & Prospects

- **Online availability since 29th October 2006**
- **Protocols for alternative methods (“cook book”)**
- **Continuously extended data collections for all toxicological areas**
- **Extension to computational toxicology**
- **ECVAM website: <http://ecvam.jrc.it>**

<http://ecvam-dbalm.jrc.it>

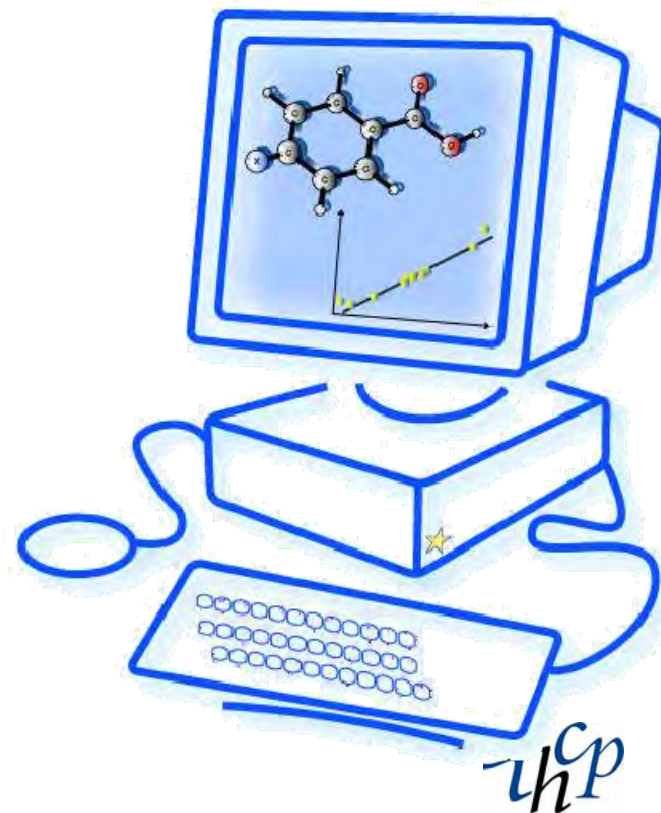


Computational Toxicology and Environmental Risk Modelling (European Chemicals Bureau)

Promoting the availability for regulatory use of valid computer-based methods

ACTIVITIES:

- **QSAR software tools for regulatory purposes** (downloadable or accessible from the ECB website: <http://ecb.jrc.it/qsar/>).
- **Case studies on QSAR validation and guidance document on QSAR validation.**
- **REACH guidance on grouping of chemicals and regulatory use of QSARs.**





lazar:

Lazy Structure-Activity Relationships

- submitted to ECVAM on 13.02.2006
- first in silico submission (2D-SAR)
- preparatory meeting in December 2006
 - validation of an endpoint, not the algorithm
 - ➡ rodent carcinogenicity
 - freeze development during assessment
 - ➡ how to address up-dates?
 - How to challenge the tool (test set)?
- ➡ expert group to develop an appropriate assessment procedure and support its application



Expert meeting

- OECD principles for (Q)SAR validation as basis
- Experts from pharmaceutical industry and academia

Objectives:

- Discussion of the need of a formal validation process for (Q)SAR models for toxicity
- Preliminary assessment of the *lazar* tool

Focus:

- Industrial chemicals
- (Regulatory) Purpose of the tool
- Completeness of required documentation and information regarding the five OECD principles

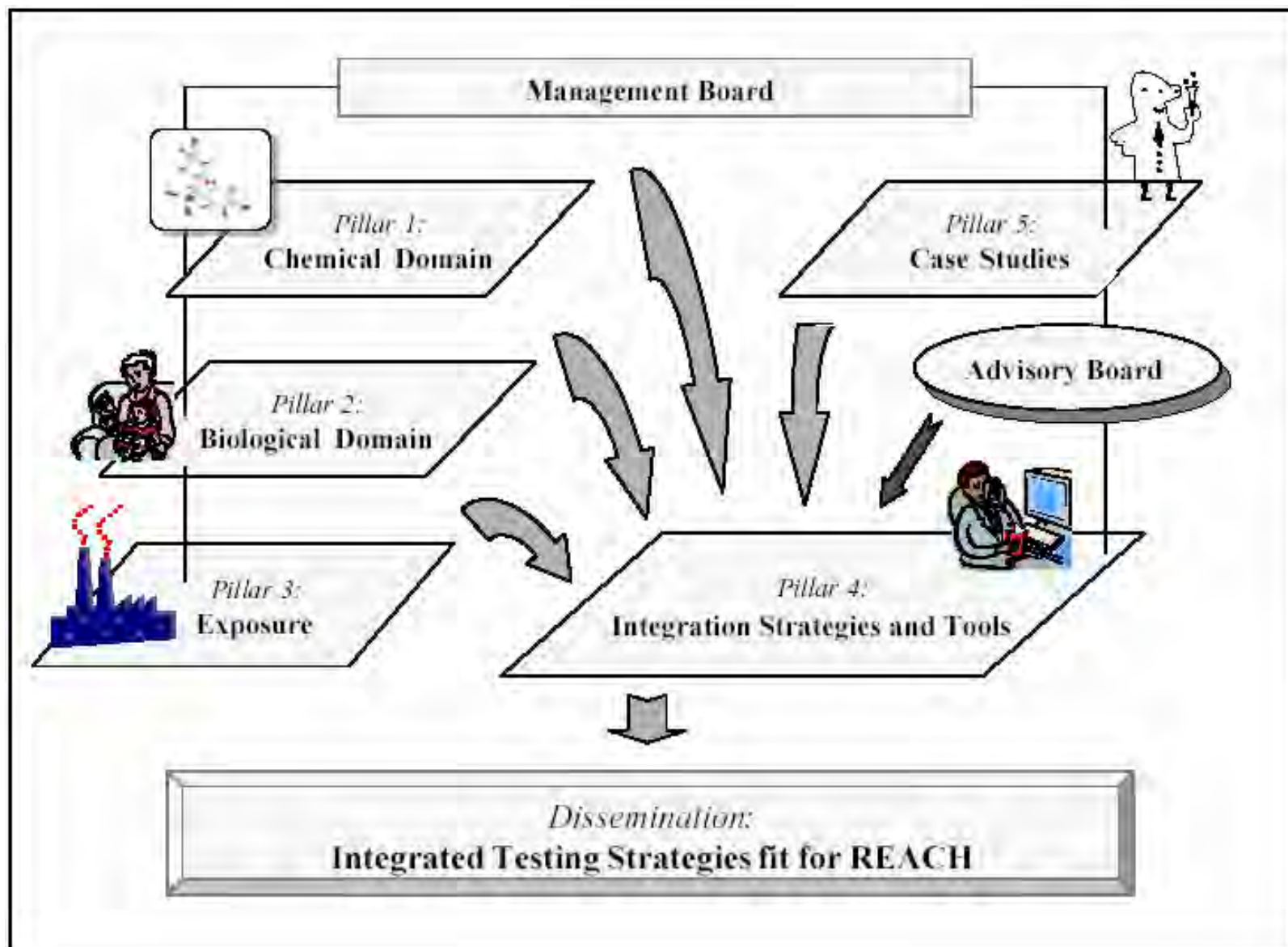


OSIRIS

Optimized Strategies for Risk Assessment of Industrial Chemicals through Integration of Non-Test and Test Information

- Integrated project of FP6 (31 partners, 10 Mio. €, 5a)
- Motivation:
Need of integrated testing strategies (ITS) for REACH
- Coordinator: G. Schürmann (UFZ Leipzig, Germany)
- ECVAM: Case study on local human health effects
- Strong involvement of ECB

OSIRIS: Structure





OSIRIS: Objectives

Development of ITS fit for REACH:

- increase the use of non-testing information for regulatory decision making
➔ reducing the need for animal studies
- transparent and sound evaluation of chemicals: risk-driven, context-specific and substance-tailored
- using read-across, *in vitro*, (Q)SAR, TTC and exposure-based waiving
- taking into account cost-benefit analyses



ECVAM Workshop Molecular Modelling Approaches for Human Hazard Assessment of Chemicals

20-22 February 2006

- homology and receptor models for endocrine disruptors (ED) and metabolism (P450)
- assessing current validation principles and their applicability to computer modelling
- Invited experts: industry, academic, regulatory; Europe, Japan, US

Evidence-based Toxicology

Validation of alternative tests is one of the rare examples of quality assurance in biomedical research (relevance, not only reproducibility)

New concept:

“Evidence-based medicine goes in vitro!”

Tools:

- Validation studies**
- Quality assurance (GLP, GCCP)**
- Systematic review & Meta-analysis**

Article: S. Hoffmann & T. Hartung „Toward an evidence-based toxicology“ Human and Exp. Tox. 2006, 25:497-513



Role model evidence-based medicine

Learning from experience may be nothing more than learning to make the same mistakes with increasing confidence.

**Petr Skrabanek, James McCormick
Follies and Fallacies in Medicine
Tarragon Press, Glasgow, 1989**

FIRST INTERNATIONAL
FORUM TOWARDS
AN EVIDENCE-BASED
TOXICOLOGY (EBT)



What ?

- DISCUSS methodologies and problems in toxicological safety assessment
- EXPLORE the available concepts of evidence-based toxicology (EBT)
- LAUNCH an initiative for formal implementation of evidence-based assessment methods

Where and when ?

- Villa Erba, Como, Italy
- October 15 to 18, 2007

How to get there ?

- <http://www.ebtox.org>



Europe goes alternative

1st Conference, Brussels, 7th Nov 2005

2nd Conference, Brussels, 18th Dec 2006

3rd Conference, planned 5th Nov 2007



- Hosted by Commissioners G. Verheugen (DG ENTR) and J. Potočník (DG JRC, DG RTD)
- **European Partnership** (7 trade associations, 27+ companies)
- Action programme

Thank you!

